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Scalable total syntheses of (−)-hapalindole U and (+)-ambiguine H

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ABSTRACT

The *Stigonemataceae* family of cyanobacteria produces a class of biogenetically related indole natural products that include hapalindoles and ambiguines. In this full account, a practical route to the tetracyclic hapalindole family is presented by way of an eight-step, enantiospecific, protecting-group-free total synthesis of (−)-hapalindole U that features an oxidative indole–enolate coupling. With gram-scale access to hapalindole U, the first total synthesis of an ambiguine alkaloid, (+)-ambiguine H, was completed via an isonitrile-assisted prenylation of an indole followed by a photofragmentation cascade.

1. Introduction: isolation and structures of complex cyanobacteria-derived indole alkaloids

The *Stigonemataceae* family of cyanobacteria produces a plethora of biogenetically related and structurally fascinating indole natural products. Comprising over 70 members, these compounds form the basis of the hapalindole,[1] fischerindole,[2] welwitindolinone,[3] ambiguine,[4] and related alkaloid classes.[5–7] In 1984, isolation efforts by Moore and co-workers opened an exciting new door in marine natural products chemistry.[1a] Isolated from soil samples found all over the world (e.g., Marshall Islands,[1a] Everglades,[5b] Australia,[2b] Micronesia,[2b,3b] Papua New Guinea,[1c] Israel[4c]), many of these natural products exhibit a broad range of biological profiles. In particular, numerous hapalindole,[1] welwitindolinone,[3] and ambiguine[4] alkaloids have shown insecticidal,[1d,2b] antialgal,[1a] antimycotic,[1a,1c,2b,4a,4c] or antibacterial[4c,8] properties. In addition, the hapalindolinones have been found to inhibit arginine vasopression binding.[5b] Finally, the welwitindolinones show anticancer activity against multiple drug resistant ovarian cancer cell lines.[9]

Although the biological activities of many of these complex alkaloids are noteworthy, it is truly their molecular structures that piqued our interest as targets for total synthesis.[6,10,11] All compounds shown in Fig. 1 are related by the presence of an indole (or indole-derived) subunit merged to a monoterpene fragment. In addition, a rather unusual isonitrile or isothiocyanate group is present in nearly all members. Finally, many of these natural products contain an asymmetric chlorine atom as well as multiple sites of further oxygenation. Moore has proposed that the entire conserved unit of these intriguing natural products (i.e., the tricyclic hapalindole core **3**) arises from an exotic chloronium (or proton) induced cyclization of tryptophan-derived isonitrile **1** with the monoterpene β-ocimene (**2**) (Fig. 2A).[2a,2b] This putative reaction forms the hallmark five continuous stereocenters unique to this alkaloid family. It should be noted, however, that nature makes many permutations of this stereochemical array (both with and without a halogen), an observation that could be attributed to imperfections in the biosynthetic machinery.[4c] From **3**, an oxidative C–C bond formation between C3 of the indole ring with the isonitrile-bearing carbon (C11) leads to the spirocyclopropyl hapalindolinone framework, a cyclization between the isopropylidene group and C2 of the indole ring furnishes the fischerindole family, and further oxidative rearrangements furnish the welwitindolinones in Moore's biosynthetic hypothesis. The tetracyclic hapalindole nucleus **4** (which nature makes in both *cis*- and *trans*-fused forms across the C10–C15 bond) is presumably formed via cyclization of the isopropylidene onto the indole C4 position.[6] Further 'reverse' prenylation of the tetracyclic hapalindoles leads to the basic ambiguine framework (**5**). Only *trans*-fused hapalindoles appear to be substrates for processing into ambiguines. Finally, an enzymatic cyclization between the isonitrile-bearing carbon (C11) and the terminus of the reverse prenyl group leads to the pentacyclic ambiguine skeleton (**6**), which represents the pinnacle of complexity in this natural product family. The recently isolated fischambiguines show divergent regiochemical preference in this late-stage cyclization, affording 6-membered rings as opposed to the usual 7-membered ambiguine carbocycles.

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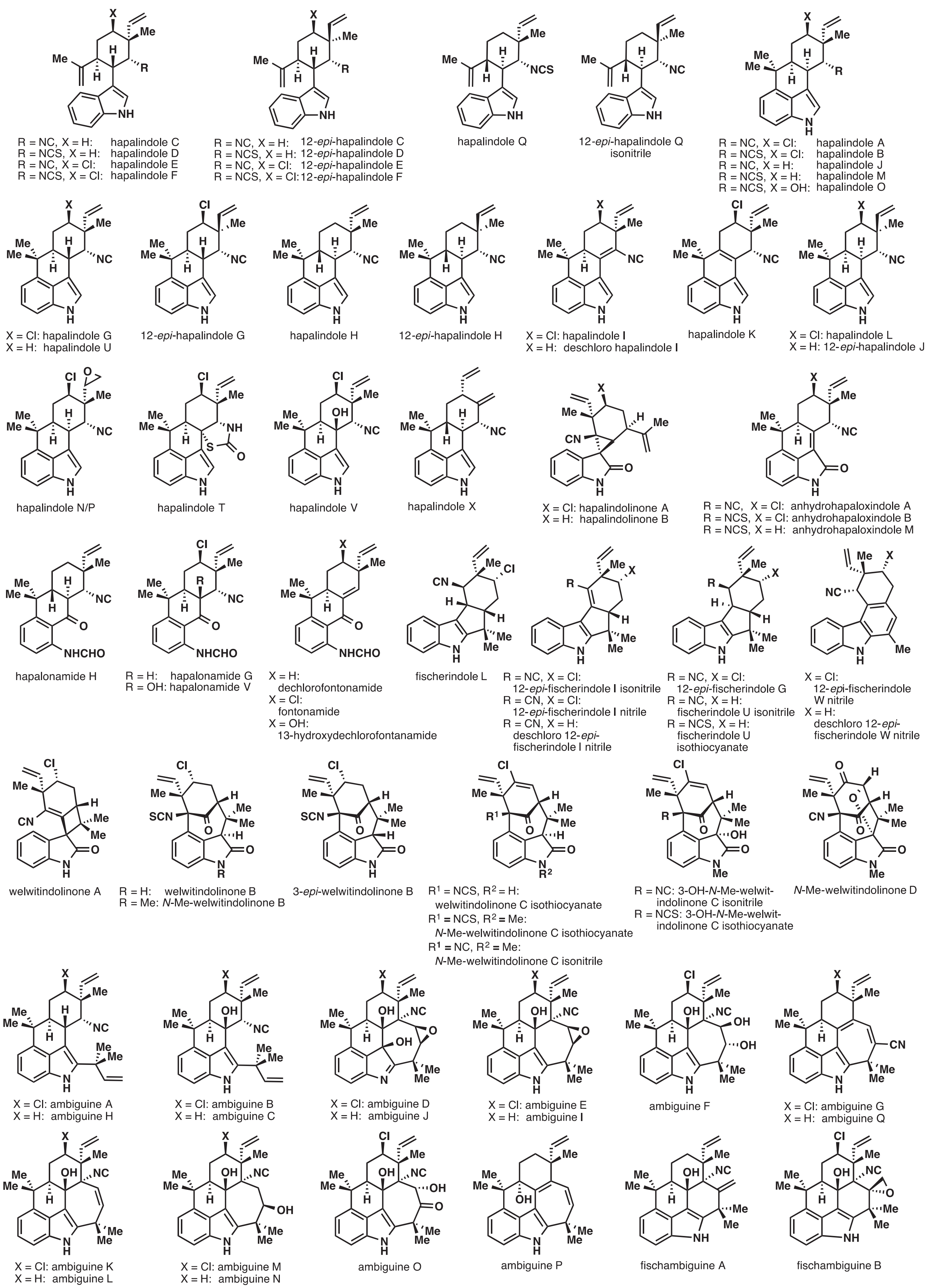

Fig. 1. Isolated members of the hapalindole family of alkaloids.

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